IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appl. No.	: 10/521,410
Applicant	: Ullrich et al.
Filed	: January 18, 2005
TC/A.U.	: 1642
Examiner	: Peter J. Reddig
Docket No.	: 2923-679
Customer No.	: 6449
Confirmation No.	: 7025

DECLARATION UNDER 37 CFR §1.132

Dear Sir:

I, Thore Hettmann, declare as follows:

1. That I have obtained a PhD degree from the University of Toronto, have completed post-doctoral training at the University of Chicago and have conducted drug development in biotech companies.

2. That I have conducted research in oncology for more than ten years and have presented and published in peer-reviewed journals.

3. That I am familiar with the subject matter described and claimed in the United States Patent Application Serial No. 10/521,410, filed on July 17, 2003, entitled "Diagnosis and prevention of cancer cell invasion", as well as the lack of enablement and written description rejections raised by the Examiner.

4. That the claims of United States Patent Application Serial No. 10/521,410 are drawn to a method of reducing the invasiveness of cancer cells by inhibiting AXL gene expression, AXL protein activity, interaction between AXL protein and its ligands, or a combination thereof.

5. That the Examiner contends that the in vivo effects described in the specification do not show a purely in vivo effect because the tumor cells were altered *in vitro* (truncation of UFO/AXL) prior to implantation. Further experimental evidence is submitted herein that shows the effects of rat anti-AXL antibodies on human prostate carcinoma growth in nude mice.

Specifically, PC-3-LN prostate carcinoma cells were orthotopically implanted into the prostate of NMRI$^{nu/nu}$ mice. The mice were randomized into 4 groups and received 25 mg/kg of the isotypic control antibody 1D5 of the antagonistic rat anti-AXL antibody 11B7, as well as 40 mg/kg Sutent or 12.5 mg/kg Taxotere. During the treatment period, the growth of orthotopically growing PC-3-LN tumors as well as peripheral metastases was monitored once weekly via in vivo bioluminescence imaging on day 15, day 23, day 29, and day 34. Compared to the isotypic control antibody 1D5, the antagonistic rat anti-AXL antibody 11B7 reduced the overall growth of PC-3-LN prostate tumors in nude mice (see Figure 1).

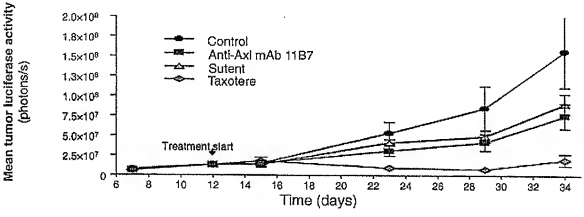

Figure 1: Mean tumor luciferase activity of human prostate carcinoma growth in nude mice undergoing treatment.

Post necropsy, selected organs (liver, spleen, lung, femur, and a part of the lumbar spine) were collected and analyzed for the presence of metastases via bioluminescence imaging. Compared to the isotypic control antibody 1D5, the antagonistic rat anti-AXL antibody 11B7 reduced the occurrence of spleen metastases. Importantly, the anti-metastatic effect of 11B7 was stronger than that of Sutent (see Figure 2).

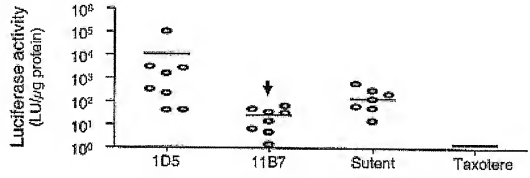

Figure 2: Effects of rat anti-AXL on human prostate carcinoma metastasis in nude mice.

6. That, as shown in the above experimental data, the claimed method demonstrates effective reduction in the invasiveness of non-altered tumor cells implanted in mice by administering an AXL inhibitor *in vivo*.

7. The undersigned further declares that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signature _____

Date June 30, 2009

THORE HETTMANN, Ph.D.

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Germany	USA

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Citizenship: German, Green Card Holder in US
Place of birth: Menden/Germany
Marital status: Married to Jacqueline Hettmann, one daughter, one son

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Current Position

Since Jan. 2005 Employer: U3 Pharma AG
Bunsenstrasse 1
D-82152 Martinsried, Germany

Position: Director, Preclinical Development

Responsibilities:
- Management of interdisciplinary preclinical oncology studies leading to IND filing and first in human trials
- Design, conductance and supervision of toxicology, safety pharmacology, pharmacokinetic and pharmacodynamic studies in rodents, dogs and primates according to current national and international guidelines
- Establishment of mouse models of targeted disease for proof of concept, target validation, in vivo efficacy, biomarker and lead selection studies
- Strategic coordination of late-stage projects for partnering with pharmaceutical partner and entry into clinical development
- Management of external collaborations (CROs and academia), MTA contracts, budget designs, SOPs and study protocols
- Presentation on project review boards with internal and external reviewers

Previous Positions

2000 - 2004	Employer:	EMD Lexigen Pharmaceuticals Billerica, MA, USA
	Position:	Senior Scientist (I and II)
	Responsibilities:	Preclinical development of conjugated antibodies and cancer vaccines against solid tumors targets Established immuno-assays to monitor tumor-specific immune responses in vivo and in vitro Scientifically evaluated optimized lead candidates for reduced toxicological profiles in animal models Contributed to teams formed around the company's principle product pipeline Strategically assessed potential IP opportunities with optimized lead candidates
1995-2000	Employer:	Harvard School of Public Health, Boston, MA and University of Chicago, Chicago, IL
	Position:	Post-Doctoral Fellow (Immunology)
	Responsibilities:	Investigated in the function of NF-κB in inflammation, apoptosis and peripheral immune cell effector functions. Created transgenic mice to analyze T cell-dependent inflammatory responses in vivo; published in top-ranked peer-reviewed journals

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Education

Dissertation

1995	Ph.D. (Immunology) Thesis: "Regulation of Human T Cell Receptor Gamma Gene Transcription"
	Conducted at the Hospital for Sick Children, Dept of Immunology and the Graduate Department of Immunology, University of Toronto, ON, Canada

Supervisors: Dr. Amos Cohen (Hospital for Sick Children, Toronto, Canada)

Certifications

2004	Certificate Biotechnology Project Management, MassBioEd, Boston, MA
2007	Certificate "Toxikologie Kompakt" at the Forum Institut für Management, Heidelberg
2008	Internet based certificates from the Postgraduate Institute for Medicine (Continuing Medical Education) with a focus on oncology and current treatment options for solid tumors

Awards

1996	National Cancer Research Institute (NCI) of Canada: Terry Fox Junior Research Fellowship (Renewed in 1998)
1994	Canadian Society for Immunology (CSI) Award.
1993	Hardi Cinader Prize from the Department of Immunology, University of Toronto
1992	Graduate Student Award from the Department of Immunology, University of Toronto.
1989	Ontario Graduate Student scholarship

University

1989-1995	Graduate studies in Immunology at the Department of Immunology, University of Immunology, Toronto, Ontario, Canada
1985-1989	Undergraduate studies in Immunology at the Department of Immunology, University of Immunology, Toronto, Ontario, Canada
1981-1984	Freie University Berlin, Teacher's College Program

School

1975-1980	High school (Gymnasium) in Rüthen/Germany; graduation (Abitur) May 1980; major: English, Physical and Health Education; minor: Biology, Mathematics
1970-1975	Secondary School (Realschule) in Belecke/Germany

1965-1970	Elementary School in Allagen/Germany

Additional work and research experiences

1989-1995	Teaching introductory immunology to first year medical students at the University of Toronto.
1989	Internship in Molecular Biology at the Venuskliniken Bonn, supervisor: Dr. Thomas Schwaab
1980-1989	Part-time tennis instructor

Further Knowledge

Data Processing	Profound knowledge of word processing, spreadsheet, presentation, statistics and communication programs; good knowledge of Linux applications
	Detailed experience with project management tools (e.g. MS Office Project) and pharmacological data processing programs (e.g. WinNonLin)
Languages	Native German Fluent in written and spoken English Knowledge of French
Personal Interests	Reading, international culture, social activities and sports

Scientific Achievements and Contributions

Publications

1. Gómez-Varela, D., Zwick-Wallasch, E., Knötgen, H., Sánchez, A., **Hettmann, T.**, Ossipov, D., Weseloh, R., Contreras-Jurado, C., Rothe, M., Stühmer, W., and Pardo, L.A. (2007). Monoclonal Antibody Blockade of Eag1 Potassium Channel Function exerts Anti-tumor Activity. Cancer Res. 67:7343.

2. Gilles, S., Lan, **Y., Hettmann, T.**, Brunkhorst, B. Reid, J. Sun Y. And Lo, K.M. A low-toxicity IL-2 based immunocytokine retains potent anti-tumor activity despite its high degree of IL-2 receptor seletivity (2007). Cancer Res. (submitted).

3. **Hettmann T.**, Opferman J.T., Leiden, J.M. and Ashton-Rickardt P.G. (2003). A Critical Role for NF-kappaB Transcription Factors in the Development of $CD8^+$ Memory-phenotype T Cells. *Immunol Lett*85:297.

4. Harding H. P., Zhang Y., Zeng H, Novoa1 I., Lu P.D., Calfon M., Sadri N., Yun C., Popko B., Paules R., F. Stojdl D.F., Bell J.C., **Hettmann T.**, Leiden, J.M. and Ron D. (2003). An integrated stress response regulates amino acid metabolism and resistance to oxidative stress. *Mol Cell* 11:619.

5. **Hettmann T.** and Leiden, J.M. (2000). NF-κB is Required for the Positive Selection of $CD8^+$ Thymocytes. *J. Immunol.* 165:5004.

6. **Hettmann T.**, Barton K. and Leiden J.M. (2000). Microphthalmia due to p53-mediated apoptosis of anterior lens epithelial cells in mice lacking the CREB-2 transcription factor. *Developmental Biology* 222:110.

7. **Hettmann T.**, DiDonato J., Karin M. and Leiden J.M. (1999). An Essential Role for Nuclear Factor κB in Promoting Double Positive Thymocyte Apoptosis. *J. Exp. Med* 189: 145.

8. **Hettmann T.** and Cohen A. (1996). Identification of an Ionomycin/Cyclosporin A responsive element within the human T cell receptor gamma enhancer. *Eur. J. Immunol.* 25:3356.

9. **Hettmann T.** and Cohen A. (1994). Identification of a T cell-specific transcriptional enhancer 3' of the human T cell receptor gamma locus. *Mol Immunol.* 31:315.

10. **Hettmann T.** and Cohen A. (1993). Analysis of Transcriptional Elelments Regulating the expression of human T cell receptor gamma genes. *J Cel Biochem.* 160:Suppl 17A

11. **Hettmann T.**, Doherty P. and Cohen A. (1992). The human T cell receptor gamma genes are transcribed from TATA-less promoters containing a conserved heptamer sequence. Mol. Immunol. 29:1073.

Patent U.S. Patent Application No.: 11/527,195 (2006); Compositions and Methods for Treating Tumors Presenting Survivin Antigens. Gillies, S., **Hettmann, T.**, Stein P. and Klinz, S.

Major scientific meetings attended

2007	Krebsforschung in München, Bio^{M} AG, Klinikum Grosshadern,
2007	AACR Annual Meeting, Los Angeles, CA
2007	The American Society of Clinical Oncology (ASCO) Annual Meeting, Chicago, IL
2006	18th EOTRC-NCI-AACR meeting in Prague, Czech Republic
2006	Krebsforschung in München, Bio^{M} AG, München
2006	Mouse Models of Cancer AACR, Cambridge, MA
2006	AACR 97th Annual Meeting, Washington, DC.
2005	The American Society of Clinical Oncology (ASCO) Annual Meeting, Orlando, FL.
2005	AACR Workshop: Accelerating Anticancer Agent Development and Validation, North Bethesda, MD.
2003	Basic Aspects of Tumor Immunology, Keystone Symposia, Keystone Colorado.
2002	Merck Lipha Sante Oncology Seminar, Lyon, France
1999	Immunobiology and Immunochemistry, Gordon Research Conferences, Lucca, Italy.
1998	T lymphocyte Activation, Differentiation and Death. Keystone, Colorado
1997	Committee on Immunology, 3rd Annual Retreat, Lake Geneva, IL.
1994	Annual Canadian Society for Immunology (CSI) meeting at Sainte-Adele, Quebec, Canada.
1993	Annual Canadian Society for Immunology (CSI) meeting at Lake Louise, Alberta, Canada